Remarks

Claims 6-12 are pending in the subject application. By this Amendment, Applicants have canceled claims 6-12 and added new claims 13-20. Support for the new claims can be found throughout the subject specification and in the claims as originally filed (see, for example, original claim 12 and "Results", pages 23-24, of the as-filed specification). Entry and consideration of the new claims presented herein is respectfully requested. Accordingly, claims 13-20 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Applicants would like to bring to the Examiner's attention a Supplemental Information Disclosure Statement (SIDS) listing references for consideration in the prosecution of the subject application. The SIDS is being submitted in conjunction with the filing of this Amendment and Applicants respectfully request that the references be considered and made of record by the Examiner in the subject application.

Claim 9 is objected to because it recites non-elected subject matter. As indicated above, claim 9 has been canceled; therefore, the objection of this claim is now moot. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 6-8 and 10-12 are rejected under 35 U.S.C. § 112, first paragraph, as non-enabled by the subject specification. The Office Action acknowledges that the specification is enabled for a polypeptide comprising the amino acid sequence of SEQ ID NO: 1, but is not enabled for polypeptides with at least 90% homology to the corresponding wild-type molecules. The Office Action argues that the specification does not provide enablement for polypeptides having at least 90% or 95-99% homology to the wild-type polypeptides and that the scope of the claims contains an unreasonable number of inoperable polypeptides which a person of ordinary skill in the art would not know how to use. The Office Action further argues that the specification does not teach, describe, or provide examples of mutant chemokines that have been further mutated and have at least 90% or 95-99% homology to the wild-type molecules and that there are no working examples in the specification of polypeptides less than 100% identical to the wild-type molecules, other than that of SEQ ID NO: 1. It is also argued that one of ordinary skill in the art would not know how to make polypeptides that still retain the necessary structural and functional activity and that the specification, while enabling for mutants as defined by SEQ ID NO: 1, is not enabling for other mutations of the

40's dibasic site or mutations of other non-40's dibasic site amino acids. The Office Action also states that the specification provides no guidance or working examples of any 40's dibasic site mutations other than SEQ ID NO: 1 and that one skilled in the art would not be able to conceive of any chemokine mutants with at least one mutation in the 40's dibasic site that would have the desired function of the claimed invention. Applicants respectfully traverse this grounds of rejection.

The test of enablement is whether one reasonably skilled in the art could make or use the invention based upon the disclosure of the patent or patent application, coupled with information known in the art, without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). Applicants also respectfully submit that the possible existence of non-operational embodiments within the scope of the claims does not necessarily mean the claims are unpatentable. *Texas Instruments v. U.S. International Trade Commission*, 805 F.2d 1558, 1562, 231 U.S.P.Q. 833, 835 (Fed. Cir 1986). "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid..." *EMI Group North America Inc. v. Cypress Semiconductor Corp.*, 60 USPQ2d 1423 (Fed. Cir. 2001); *Atlas Powder Co. v. E.I. Du Pont De Nemours Co.*, 750 F.2d 1569, 1576-77, 224 U.S.P.Q. 409, 414 (Fed. Cir. 1984). Further, enablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed invention, *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 960, 220 U.S.P.Q. 592, 599 (Fed. Cir. 1983), and is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive. *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 U.S.P.Q. 409, 413 (Fed. Cir. 1984); *W.L. Gore and Associates v. Garlock, Inc.*, 721 F.2d 1540, 1556, 220 U.S.P.Q. 303, 315 (Fed. Cir. 1983). Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. Indeed, actual working examples are not required by the patent laws. *In re Borkowski*, 422 F.2d 904, 908, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970). Further, the quantity of experimentation can be "considerable", "tedious", "laborious", and "time-consuming" as long as the experiments are merely "routine". See *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (B.P.A.I. 1982) ("[t]he test [of enablement] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine."); see also *Ex parte Erich* 3 U.S.P.Q.2d 1011 (B.P.A.I. 1982). Additionally, the analysis of whether the

claims are supported by an enabling disclosure requires a determination of whether the disclosure contains sufficient information regarding the subject matter of the claims so as to enable one skilled in the pertinent art to make and use the claimed invention. Applicants, thus, respectfully submit that one skilled in the art would have been able to make and use this invention, without undue experimentation, based upon the disclosure of this application and information known in the art at the time this application was filed.

The RANTES homologs disclosed in this application are antagonists of the wild-type RANTES polypeptide. Applicants submit that the specification teaches a variety of polypeptides having at least 90% homology to the corresponding wild-type polypeptides (see Table 1, page 25) and also sets forth methods of making such polypeptides (see, page 14, first full paragraph). Further, as indicated in paragraphs 11-17 of United States Patent Application Publication No. US 2004/0101509, the structural requirements and functional effects of GAG-RANTES interactions have been studied in a variety of models. These models have identified regions of the RANTES polypeptide associated with GAG interactions (amino acids 44-47 and 55-66). Additionally, it was known in the art that N-terminal truncation variants of RANTES were antagonists of the naturally occurring RANTES form as was a variant to which an N-terminal methionine was added ('509 application at paragraphs 5-7). Lusso and Polo (WO 99/33989) also teach a number of portions of the RANTES polypeptide that can be modified via amino acid substitutions as well as a variety of RANTES variant polypeptides (see page 3, line 1 through to page 4, line 4). Thus, one skilled in the art would have known those portions of the RANTES polypeptide that could be modified to achieve a desired effect (*e.g.*, interference with, or the reduction of, GAG-RANTES interactions or antagonism of the chemokine effects associated with wild-type RANTES).

This knowledge, coupled with the teachings of the specification, would have enabled one skilled in the art to make and use RANTES polypeptides having at least 90% identity to the wild-type RANTES polypeptide and having reduced GAG binding activity without undue experimentation. Further, such polypeptides would have had no more than six or seven amino acid substitutions/deletions as compared to the mature wild-type RANTES polypeptide (a polypeptide of 68 amino acids). While the screening of such polypeptide variants might be considered "tedious", "laborious", and "time-consuming", it is, nonetheless, routine and would not constitute "undue

experimentation" under the patent laws. Accordingly, Applicants respectfully submit that the claimed invention is enabled by the teachings of the subject specification, coupled with information known in the art, and that one skilled in the art would have been able to practice the claimed invention without undue experimentation.

Claims 6-8 and 10-12 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully assert that there is adequate written description in the subject specification to convey to the ordinarily skilled artisan that they had possession of the claimed invention. The Office Action also argues that the specification does not teach what changes can be made to the wild-type molecules while maintaining the desired structure and function of the wild-type molecules. The Office Action further argues that the specification fails to identify those amino acids that can be mutated or changed while still retaining the structure and function of the wild-type molecules. Finally, the Office Action argues that the claims do not require that the polypeptides or polynucleotides recited within the claims possess any particular biological activity or have any other distinguishing feature other than having at least 90% or 95-99% homology to wild-type molecules. Applicants respectfully traverse.

As the Patent Office is aware, the standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The Enzo court adopted the standard that "the written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'" See *Enzo Biochem, Inc. v. Gen-Probe Inc.*,

296 F.3d 1316, 1324, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). The court in Enzo adopted its standard from the Patent Office's Written Description Examination Guidelines. See 296 F.3d at 1324, 63 U.S.P.Q.2d at 1613 (citing the Guidelines).

The specification specifically describes the chemical structure of a number of polypeptides that have at least 90% homology to the wild-type RANTES polypeptide and which exhibit reduced GAG binding as compared to the wild-type RANTES polypeptide (see SEQ ID NOs: 1-9, Table 1, and specification at page 8, first full paragraph). The complete unaltered sequence of the RANTES polypeptide was also known in the art and was provided in the as-filed specification (SEQ ID NO: 10; Table 1). Applicants further submit that the as-filed specification also indicates that, in addition to amino acids 44, 45 and 47, amino acid 32 could be substituted in the RANTES polypeptide to arrive at a polypeptide having reduced GAG binding activity (see SEQ ID NOs: 4 and 6 and page 8, first full paragraph). Thus, it is respectfully submitted that Applicants have provided a complete structure for altered polypeptides falling within the scope of the recited claim and the structure of the wild-type mutant to which amino acid alterations can be made.

Applicants also submit that the regions of the RANTES polypeptide associated with GAG interactions were known in the art (amino acids 44-47 and 55-66; see paragraphs 13-15 of United States Patent Application Publication No. US 2004/0101509). Indeed, the as-filed specification discloses a number of polypeptides that contain alterations in the 40's dibasic loop (amino acids 44-47) of the wild-type RANTES polypeptide and that exhibit reduced GAG binding. Thus, there was a known or disclosed correlation between structure and function of the RANTES molecule, namely alterations at amino acids 44-47 and/or 55-66 would result in the formation of RANTES homologs that had reduced GAG binding. Thus, Applicants submit that the recited functional characteristics (*e.g.*, decreased GAG binding) coupled with the known correlation between the structure and function of the RANTES polypeptide, the knowledge of other homologs of RANTES having reduced GAG binding, and the sequence/structure of the wild-type RANTES polypeptide would have allowed one skilled in the art to recognize that Applicants invented the claimed subject matter, including homologs having reduced GAG binding activity and at least 90% homology to the wild-type RANTES polypeptide. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 6-12 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite in the recitation of the term "muteins." Applicants respectfully assert that the claims as filed are definite. However, by this Amendment, claims 6-12 have been canceled, thereby rendering this rejection moot. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

Claims 6-8, 10 and 11 are rejected under 35 U.S.C. §102 (b) as anticipated by Lusso and Polo (WO 99/33989). Applicants respectfully assert that the Lusso and Polo reference does not anticipate the claimed invention and is moot in view of the cancellation of these claims. Applicants further note that the new claims are not anticipated by Lusso and Polo, relating to RANTES mutants and therapeutic applications thereof. Lusso and Polo disclose (on page 5) various routes of administration, namely by the parenteral, sublingual, intranasal, inhalatory, or topical routes. Applicants note, however, that the reference is completely silent about oral administration. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

Claims 6-9 and 11 are rejected under 35 U.S.C. § 102(b) as anticipated by Proudfoot *et al.* (2001). Applicants respectfully assert that the Proudfoot *et al.* reference does not anticipate the claimed invention and that the rejection is now moot in view of the cancellation of the claims. Applicants note that the new claims are not anticipated by the Proudfoot *et al.* reference since it discloses that the RANTES mutant ^{44}RKNR^{47} has reduced GAG binding activity; however, the reference is silent about pharmaceutical uses of the mutant and administration routes. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

Claim 12 is rejected under 35 U.S.C. § 103(a) as obvious over Lusso and Polo (WO 99/33989) in view of Strieter *et al.* (U.S. Patent No. 5,871,723). Applicants respectfully assert that the claimed invention is not obvious over the cited references, whether taken alone or in combination. As noted above, the Lusso and Polo reference discloses a variety of routes for the administration of RANTES mutants; however, the reference is silent about oral administration of such RANTES mutants. Strieter *et al.* mention administration of CXC chemokines for inhibiting angiogenesis. The oral route of administration is first mentioned in column 14, lines 31-49, where it is stated that ingestible formulations for the treatment of gastric or duodenal cancers may be used.

However, column 47, lines 38-49, makes clear that oral administration is only considered in Strieter *et al.* under certain conditions, namely, for chemically designed or modified agents, dextrorotatory peptidyl agents, liposomal formulations and formulations in time release capsules to avoid peptidase and lipase degradation. Applicants also submit that a person of ordinary skill in the art would not have been motivated to combine the Strieter *et al.* patent with Lusso and Polo because the teachings of Strieter *et al.* relate to CXC chemokines as opposed to the CC chemokines taught in Lusso and Polo. Further, Strieter *et al.* imply that chemokines must be chemically or mechanically protected against degradation in order to be orally administered; thus, an ordinarily skilled artisan would not apply Strieter *et al.* to the chemokine mutants disclosed in Lusso and Polo, particularly since Lusso and Polo are completely silent about such a route of administration. Thus, Applicants respectfully submit that one skilled in the art would not have been motivated to combine the teachings of Lusso and Polo with those of Strieter *et al.* and respectfully request reconsideration and withdrawal of the obviousness rejection.

While Applicants respectfully submit that a *prima facie* case of obviousness has not been established by the Patent Office, Applicants further submit that the subject application surprisingly shows, in the examples, that RANTES homologs, such as SEQ ID NO: 1 have increased oral bioavailability and effectiveness as compared to wild-type RANTES polypeptides and/or the same RANTES homolog provided to a test subject via a different route of administration. It is respectfully submitted that such increased bioavailability and effectiveness would not have been expected by one skilled in the art in view of the teachings of the cited references and that these examples and data provide evidence pertaining to the non-obviousness of the claimed invention.

The specification clearly indicates that RANTES homologs having reduced GAG-binding activity and non-conservative substitutions in the 40's dibasic site exhibit increased bioavailability and better efficacy when administered orally (see, for example, Results, pages 23-24 of the as-filed specification). As indicated therein, RANTES homologs having non-conservative substitutions in the 40's dibasic site were able to exert an antagonistic activity for a longer period of time when administered orally. The passages of these pages also indicate that RANTES homologs were able to inhibit cell recruitment in the peritoneal cavity of animals when administered orally and intraperitoneally. However, a time course study indicated that orally administered RANTES

homologs (having a reduced GAG-binding activity and non-conservative mutations in the 40's dibasic site) inhibited the recruitment of peritoneal cells by RANTES for up to 24 hours whereas the same intraperitoneally administered RANTES homolog was able to inhibit the recruitment of cells for a period of less than 8 hours. Thus, the oral administration of RANTES homologs has been demonstrated to have unexpectedly better bioavailability and/or ability to inhibit the recruitment of cells as compared to other routes of administration (*e.g.*, intraperitoneal administration) for the same RANTES homolog. Applicants respectfully submit that this is an unexpected benefit of the oral administration of the claimed RANTES homologs and, accordingly, request reconsideration and withdrawal of the obviousness rejection of record. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 6-12 are rejected under the judicially created doctrine of "obviousness-type" double patenting over claims 1-5 and 9 of co-pending U.S. application Serial No. 10/398,457. While Applicants acknowledge that a Terminal Disclaimer can be filed to overcome this rejection, it is submitted that a double patenting rejection of the obviousness-type is analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103, except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 U.S.P.Q. 29 (C.C.P.A. 1967). Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 U.S.P.Q.2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985). Accordingly, the analysis employed in an obviousness-type double patenting determination parallels the guidelines for a 35 U.S.C. 103(a) rejection and the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966) are applied for establishing a background for determining obviousness under 35 U.S.C. 103, including the consideration of any indicia of non-obviousness, when making an obvious-type double patenting analysis (emphasis added). Further, any obviousness-type double patenting rejection should make clear the differences between the inventions defined by the conflicting claims and the reasons why a person of ordinary skill in the art would conclude that the invention defined in the claims of the pending application at issue would have been an obvious variation of the invention defined in a claim in the patent.

In this instance, Applicants respectfully submit that the as-filed specification provides evidence pertaining to the non-obviousness of the claimed invention and that the application of an obviousness-type double patenting rejection in this matter is inappropriate For example, the specification clearly indicates that RANTES homologs having reduced GAG-binding activity and non-conservative substitutions in the 40's dibasic site exhibit increased bioavailability and better efficacy when administered orally (see, for example, Results, pages 23-24 of the as-filed specification). As indicated therein, these types of RANTES homologs were able to exert an antagonistic activity for a longer period of time when administered orally. The data and discussion contained herein also indicate, in a time course study, that orally administered RANTES homologs having a reduced GAG-binding activity inhibited the recruitment of peritoneal cells by RANTES for up to 24 hours whereas the same intraperitoneally administered RANTES homolog was able to inhibit the recruitment of cells for a period of less than 8 hours. Thus, the oral administration of RANTES homologs has been demonstrated to have unexpectedly better bioavailability and/or ability to inhibit the recruitment of cells as compared to other routes of administration (*e.g.*, intraperitoneal administration) for the same RANTES homolog. Accordingly, it is respectfully requested that these indicia of non-obviousness be taken into consideration and that the obviousness-type double patenting rejection of record be withdrawn.

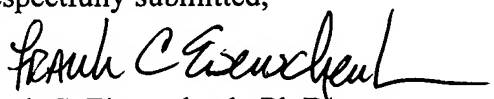
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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